Discussion of the Obviousness Rejection as Regards Claims 1-8

According to the Office Action, US '193 teaches citalopram derivatives of the type recited in pending claims 1-8 (col. 2, lines 12-29). The Office Action concedes, however, that US '193 does not teach the particle size or average aspect ratio recited in pending claims 1-8. The Office Action states that UK '762 teaches analogous citalopram derivatives with particles sizes within the claimed ranges (page 13, lines 5-14) and contends it would have been obvious to apply the teachings of UK '762 to the compounds disclosed in US '193. Applicants traverse the rejection.

The method disclosed in UK '762 includes passing citalopram base through a sieve with 0.3 mm holes (see page 13, lines 5-14). However, it should be noted that the text passage the Office Action points to in UK '762 for disclosing a specific particle size pertains to the preparation of citalopram-containing tablets, and not the preparation of crystals of citalopram hydrobromide per se as in connection with the present invention. It is not at all clear that this disclosure can be applied to crystals of citalopram hydrobromide. Moreover, even if the method could be used to prepare crystals of citalopram hydrobromide, the crystals obtained after passing through such a sieve would not necessarily have the particle sizes recited in pending claims 1-5. The range of crystal sizes would certainly vary between particles much smaller than 5 μm and those much larger than 5 μm but with absolutely no control over the total percentage of particles of 5 μm or less. Moreover, the use of such a sieve does not allow the adjustment of the aspect ratio of the particles to the specific values recited in pending claims 3-8.

The Office Action contends that one of ordinary skill in the art could surmise that useful properties such as those of the present invention as defined by pending claims 1-8 could be realized from the teachings of UK '762 (page 2, fourth paragraph). In fact, neither US '193 nor UK '762 teaches or suggests citalopram hydrobromide crystals in which up to 35% of the crystals have a particle size of 5 μm or less (claims 1-5) or particular average aspect ratios (claims 3-8). Indeed, nothing in either of these references would suggest that such crystals are even made. Since no special precautions are taken in the method disclosed in UK '762 to prepare such crystals, it cannot even be said that the properties of the present invention are inherent to the product formed by the Office Action's suggested combination of US '193 and UK '762. Thus, there is a lack of a suggestion in the art to combine the cited references, and the combination of the cited references in any event fails to disclose all the elements of the claims.

Accordingly, the present invention as defined by pending claims 1-8 must be considered unobvious in view of the disclosures of US '913 and UK '762. The section 103(a) rejection of pending claims 1-8 should be withdrawn.

Discussion of the Obviousness Rejection as Regards Claims 9-19

The Office Action asserts that UK '762 teaches a method of preparing crystalline citalopram as recited in pending claims 9-19, but concedes that UK '762 does not disclose using acetone. The Office Action alleges Ram uses acetone in the preparation of citalopram and suggests it would have been obvious to use acetone in the method taught by UK '762, especially since acetone is produced *in situ* in the method of UK '762 (page 5, lines 15-19). Applicants traverse the rejection.

UK '762 discloses the preparation of a citalopram salt that includes precipitating the citalopram base in crystalline form, optionally recrystallizing the crystalline citalopram, and converting the crystals to a salt (see page 3, lines 1-6). The method for converting the citalopram base to a salt includes reacting the base with acid in a water miscible salt such as acetone or ethanol (see page 5, line 33, through page 6, line 3). However, UK '762 does not proceed to disclose a method of crystallizing the obtained citalopram hydrobromide. Thus, crystallizing the obtained citalopram hydrobromide -- with any solvent, let alone a C_1-C_3 alcohol, water, or acetone as recited in pending claims 9-19 -- is not disclosed anywhere in UK '762.

In addition, applicants fail to see how acetone would be made *in situ* in the method disclosed in UK '762 as alleged in the Office Action. According to UK '762, citalopram derivatives containing an acetate group ($CH_3C(O)O^-$) can be removed as an impurity from the citalopram base (page 3, line 19, through page 4, line 9). Depending on the reagents used, removal of the acetate group would form either an acetate salt (e.g., $CH_3C(O)ONa$) or acetic acid ($CH_3C(O)OH$) -- not acetone ($CH_3C(O)CH_3$).

Ram relates to a method for radiolabeling citalopram by reacting desmethylcitalopram with $^{11}CH_3I$ and NaOH in acetone. Nothing in Ram teaches or suggests crystallizing citalopram hydrobromide with acetone, or for that matter a C_1-C_3 alcohol or water, as recited in pending claims 9-19.

Since UK '762 and Ram are directed to different objectives, there would have been no motivation for one of ordinary skill in the art to combine their respective disclosures at the relevant time. Moreover, even if the disclosures of UK '762 and Ram are combined, the present invention as recited in pending claims 9-19 would not result, because both references lack any teaching or suggestion of crystallizing citalopram hydrobromide, let alone crystallizing citalopram hydrobromide with a C_1-C_3 alcohol, water, or acetone.

Accordingly, the present invention as defined by pending claims 9-19 must be considered unobvious in view of the disclosures of UK '762 and Ram. The section 103(a) rejection of pending claims 9-19 should be withdrawn.

Information Disclosure Statement

Applicants submitted an Information Disclosure Statement dated October 10, 2001, which included a PTO-1449 form identifying references AB-AE. Applicants request a copy of the PTO-1449 form with the Examiner's initials thereon, thereby confirming the Examiner's consideration of references AB-AE. In addition, applicants submit herewith an Information Disclosure Statement which include a PTO-1449 form identifying references AF-AG. Applicants request a copy of the PTO-1449 form with the Examiner's initials thereon, thereby confirming the Examiner's consideration of references AF-AG.

Conclusion

The application is considered to be in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

John Kilyk, Jr., Reg. No. 30,763
One of the Attorneys for Applicant(s)
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 North Stetson
Chicago, Illinois 60601-6780
(312) 616-5600 (telephone)
(312) 616-5700 (facsimile)

Date: April 29, 2002

In re Appln. of Ikemoto et al.
Application No. 09/824,447

CERTIFICATE OF MAILING

I hereby certify that this RESPONSE TO OFFICE ACTION (along with any documents referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231.

Date: April 29, 2002

M:\Clients\Takeshima\Amd\210485am1.DOC